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Synthesis, crystal structure and antimalarial activity of novel 1,2,5,6-tetraoxacycloalkanes from 2,3-dihydroperoxy-2-phenylnorbornane

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Abstract

Photooxygenation of 2-phenylnorbornene **1** in the presence of 30% aqueous hydrogen peroxide in acetonitrile afforded the labile 1,2-bis-hydroperoxide **3** which could be cycloalkylated to provide the tricyclic peroxides **5**, albeit in low yield, on treatment with silver oxide and a 1,ω-diiodoalkane. Trimethylsilylation of **3**, followed by TMSOTf-catalyzed cyclocondensation with carbonyl compounds led to the formation of the tricyclic peroxides **8** containing a 1,2,4,5-tetroxepane structure. The structures of two novel tricyclic peroxides **5a** and **8a** were unambiguously determined by the X-ray crystallographic analysis.

Since malaria parasites are rapidly developing resistance to the most commonly used chemotherapeutic alkaloidal drugs, the antimalarial properties of nonalkaloidal compounds such as artemisinin and the related endoperoxides have attracted considerable attention.[1] We have recently reported that treatment of (alkylidene)bis-hydroperoxides with 1,ω-dihaloalkanes in the presence of CsOH in DMF[2] affords a series of novel 1,2,4,5-tetraoxacycloalkanes which exhibit remarkable antimalarial activity in vitro.[3] In the development of new synthetic routes to cyclic peroxides containing two peroxide groups within the same ring, the comparatively rare *vic*-bis-hydroperoxides were identified as promising precursors.[4]

2-Phenylnorbornene **1** is known to react with singlet oxygen to generate a zwitterionic intermediate which can be efficiently trapped by methanol to form **2**.[5] By analogy, photooxygenation of **1** in the presence of 30% aq. hydrogen peroxide in acetonitrile afforded the bis-hydroperoxide **3** in essentially quantitative yield.[6] Since compound **3** was labile toward silica gel, it was used without further purification. The *cis*-1,2-diol **4** was obtained by reduction of **3** with triphenylphosphine (Scheme 1).

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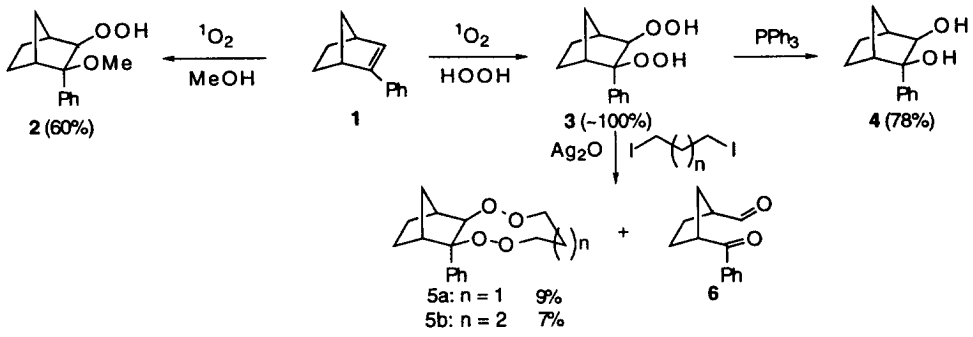


Scheme 1.

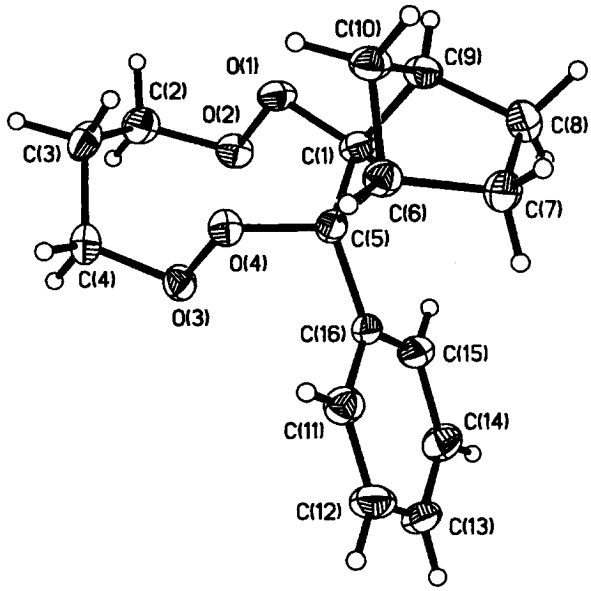
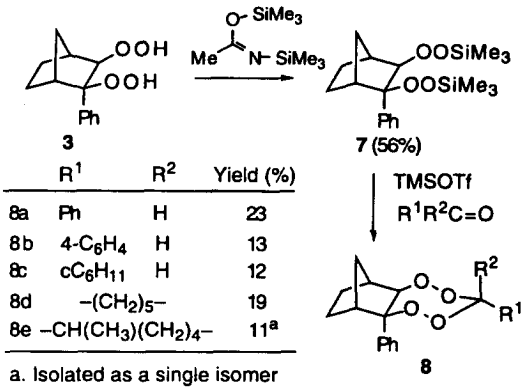


Figure 1. The structure of one molecule of **5a** (there are two independent molecules of **5a** per asymmetric unit which exhibit only minor structural differences)

In contrast to the (alkylidene)bis-hydroperoxides,[3] when the bis-hydroperoxide **3** was treated with 1,3-diiodopropane in the presence of CsOH, none of the expected tricyclic peroxide **5a** was formed; only the keto aldehyde **6** was isolated.[7] In an alternative approach, treatment of a mixture of **3** and 1,3-diiodopropane with Ag_2O[8] in CH_2Cl_2 gave the desired tricyclic peroxide **5a**, containing a 1,2,5,6-tetroxecane ring, albeit in low yield.[9] The major by-product was the keto aldehyde **6** (48%). The 1,2,5,6-tetroxecane derivative **5b** was obtained from the analogous reaction involving 1,4-diiodo-butane.

In the crystal structure of **5a**, as determined by the X-ray analysis (Fig. 1),[10] the nine-membered tetroxecane ring adopts the symmetrical boat–chair conformation (cf. the 1,2,4,5,7,8-hexox-ecanes[11] and 1,2,4,5-tetroxecanes[3] which adopt the [333] twist–boat–chair conformations).

Although the bis-hydroperoxide **3** was acid-labile, it was successfully transformed using *N,O*-bis(trimethylsilyl)acetamide into the corresponding bis-trimethylsilylated derivative **7**[12] which subsequently underwent TMSOTf-catalyzed cyclocondensation with carbonyl compounds to provide a series of novel 1,2,4,5-tetroxepane derivatives **8a–e** (Scheme 2).[13] The by-product was again the keto aldehyde **6**.



	R^1	R^2	Yield (%)
8a	Ph	H	23
8b	4-C_6H_4	H	13
8c	cC_6H_{11}	H	12
8d	$-(CH_2)_5-$		19
8e	$-CH(CH_3)(CH_2)_4-$		11[a]

a. Isolated as a single isomer

Scheme 2.

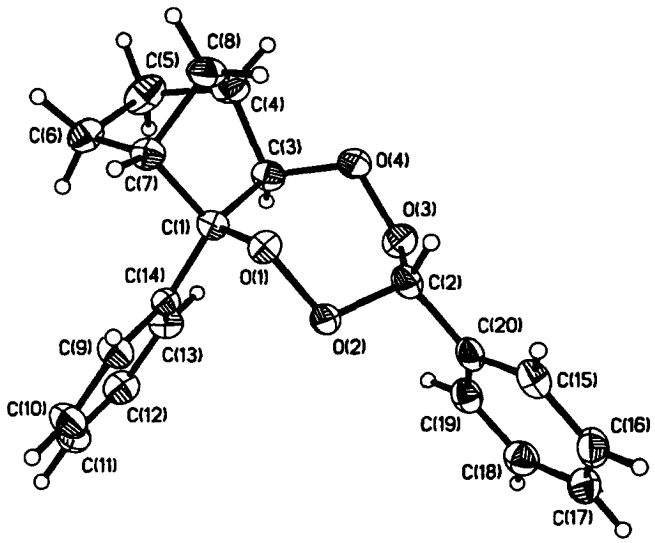


Figure 2. The crystal structure of compound **8a**

The crystal structure of **8a**, as determined by the X-ray analysis, is depicted in Fig. 2.[10] The 1,2,4,5-tetroxepane ring of **8a** is in a chair conformation with the phenyl group at C(2) in a pseudo-equatorial position. Corresponding geometrical parameters in the structures of compounds **5a** and **8a** are in reasonable agreement. The somewhat idealized conformations observed for the peroxide rings in **5a** and **8a** arguably arise from the restrictions imposed on the system by the rigid, fused bicyclo[2.2.1]heptane moiety.

In a preliminary study of the antimalarial activities of the derived cyclic peroxides **5** and **8** against *P. falciparum*,[14] compounds **5a** and **8e** provided EC_{50} values 1.9×10^{-7} M and 1.3×10^{-7} M, respectively, which are approximately 20 times less potent than artemisinin (7.8×10^{-9} M).

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6. A cooled (0°C), oxygenated solution of **1** (290 mg, 1.71 mmol), 30% aqueous H_2O_2 (10 g), and tetraphenylporphine (1 mg) in CH_3CN (20 cm^3) was irradiated for 1.5 h with a 300 W high-pressure mercury lamp through an aqueous $CuSO_4$ filter solution (>400 nm). After extraction with Et_2O (50 ml), the organic layer was washed in turn with aq. $NaHCO_3$ and saturated brine. Removal of solvent (room temp., 15 mmHg) to yield the crude 1,2-bis-hydroperoxide **3** as the sole product. 2,3-Dihydroperoxy-2-phenylnorbornane **3**: an oil; ^1H NMR ($CDCl_3$) δ 0.8–1.5 (m, 5H), 2.1–2.2 (m, 1H), 2.4–2.5 (m, 1H), 2.5–2.6 (m, 1H), 4.77 (s, 1H), 7.1–7.5 (m, 5H), 8.52 (br s, 1H), 10.12 (br s, 1H); ^{13}C NMR δ 23.56, 25.12, 34.81, 41.71, 46.18, 91.16, 95.65, 128.09, 128.27 (2C), 128.52 (2C), 138.54.
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9. To a stirred solution of 1,3-diiodopropane (890 mg, 3 mmol) and Ag_2O (510 mg, 2.2 mmol) in CH_2Cl_2 (25 cm^3), was added bis-hydroperoxide **3** (472 mg, 2.0 mmol) by syringe over 10 min. The resulting mixture was stirred at rt for 16 h. The products were subsequently isolated by column chromatography on silica gel, eluting initially with Et_2O:hexane (4:96) to give tetroxane **5a** (50 mg, 9%) followed by Et_2O:hexane (3:7) to give keto aldehyde **6** (194 mg, 48%). 2-Phenyl-3,4,8,9-tetraoxatricyclo[9.2.1.$0^{2,10}$]tetradecane **5a**: mp 140–142°C (from methanol); ^1H NMR ($CDCl_3$) δ 1.1–1.6 (m, 6H), 2.18 (d, *J*=10.2 Hz, 1H), 2.3–2.4 (m, 1H), 2.4–2.5 (m, 1H), 2.9–3.0 (m, 1H), 3.93 (dt, *J*=10.2 and 10.2 Hz, 2H), 4.42 (d, *J*=10.2 Hz, 2H), 4.74 (s, 1H), 7.2–7.6 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.03, 24.82, 25.27, 35.65, 42.81, 47.93, 73.66, 73.96, 87.17, 93.82, 127.39 (2C), 128.30 (2C), 128.37, 140.17. Anal. calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.10; H, 7.26.
10. X-Ray diffraction data were collected on a Siemens P4 diffractometer at 160 K using graphite monochromated Mo-K_α λ=0.71073 Å. The structures were solved by direct methods and refined using least-squares techniques. [SHELXTL (Vers 5.1), Sheldrick, G. M. Brucker AXS: Madison, WI, USA.] Crystal data for **5a**: $C_{16}H_{20}O_4$, *M*=276.32, triclinic, $P\bar{1}$, *a* 9.6120 (10), *b* 911.6600 (10), *c* 12.3820 (10) Å, α 86.310 (10), β 89.900 (10), γ 89.930 (10)°, *U* 1384.8 (2) $Å^3$, *Z*=4, D_c 1.325 g cm^{-3}, F(000) 592, μ(Mo-K_α) 0.094 mm^{-1}. Final discrepancy factors: *R*=0.050 and wR^2=0.095. Crystal data for **8b**: $C_{20}H_{20}O_4$, *M*=324.36, monoclinic, $P2_1/c$ (no. 14), *a* 6.0166 (6), *b* 17.2801 (10), *c* 15.6010 (11) Å, β 94.079 (9)°, *U* 1617.9 (2) $Å^3$, *Z*=4, D_c 1.332 g cm^{-3}, *F*(000) 688, μ(Mo-K_α) 0.092 mm^{-1}. Final discrepancy factors: *R*=0.039 and wR^2=0.094.
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13. This procedure is based on: Jefford, C. W.; Jaber, A.; Boukouvalas, J. *Synthesis* **1988**, 391. To a stirred solution of peroxide **7** (322 mg, 0.85 mmol) and benzaldehyde (180 mg, 1.70 mmol) in CH_2Cl_2 (25 cm^3) was added TMSOTf (111 mg, 0.5 mmol) by syringe over 10 min at −70°C. Stirring was continued at 0°C for further 1.5 h. The products were isolated by column chromatography on silica gel, eluting initially with Et_2O:hexane (1:25) to give the tetroxepane **8a** (64 mg, 23%) and subsequently with Et_2O:hexane (1:9) to give keto aldehyde **6** (62 mg, 36%). 2,5-Diphenyl-3,4,6,7-tetroxatricyclo[7.2.1.$0^{2,8}$]dodecane **8a**: mp 133°C (from ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$) δ 0.9–1.0 (m, 1H), 1.1–1.4 (m, 3H), 1.5–1.6 (m, 1H), 2.3–2.4 (m, 2H), 2.5–2.6 (m, 1H), 5.21 (s, 1H), 6.65 (s, 1H), 7.1–7.7 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 23.76 (CH_2), 23.87 (CH_2), 35.08 (CH_2), 41.42 (CH), 47.12 (CH), 91.45 (CH), 98.62, 109.33 (CH), 127.12 (2C, CH), 127.42 (CH), 127.48 (CH), 127.69 (CH), 128.21 (CH), 128.41 (2C, CH), 128.79 (CH), 130.05 (CH), 130.67, 139.87. Anal. calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.22. Found: C, 74.15; H, 6.25.

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